PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
CHARLES E. STEFFEY
SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	06 JAN 2005
Applicant's or agent's file reference: 1662.005WO1	REPLY DUE: within 1 months/days from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/37677	24 November 2003 (24.11.2003)	27 November 2002 (27.11.2002)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): C12Q 1/70; G01N 33/53; A61K 39/395, 39/12 and US Cl.: 435/5, 7.1, 7.1; 424/130.1, 204.1

Applicant

NATIONAL INSTITUTES OF HEALTH

DV 6 FEB. 2005

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2 (a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension. See rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 27 February 2005 (27.02.2005).

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Stacy B. Chen Valerie Bell-Harris for Telephone No. (571) 272-1600

Form PCT/IPEA/408 (cover sheet)(July 1998)

WRITTEN OPINION

International application No.
PCT/[illegible]03/37677

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-58, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the claims:
pages 59-71, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☒ the drawings:
pages 1-3, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE _____

☐ the claims, Nos. NONE _____

☐ the drawings, sheets/~~fig~~ NONE _____

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."*

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Inventive Step (IS)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO
Industrial Applicability (IA)	Claims Please See Continuation Sheet	YES
	Claims Please See Continuation Sheet	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:
The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

V.1. Reasoned Statements:
The opinion as to Novelty was positive (Yes)with respect to claims 7-11,38-41,44,46-58,64,68,73-75,87-89,98-100,110,114,115,128
The opinion as to Novelty was negative (No) with respect to claims 1-6,12-37,42,43,45,59-63,65-67,69-72,76-86,90-97,101-109,111-113,116-127,129
The opinion as to Inventive Step was positive (Yes)with respect to claims NONE
The opinion as to Inventive Step was negative(NO) with respect to claims 1-129
The opinion as to Industrial Applicability was positive (YES) with respect to claims 1-129
The opinion as to Industrial Applicability was negative(NO) with respect to claims NONE

V. 2. Citations and Explanations:
Claims 1-6, 12-37, 42, 43, 45, 59-63, 65-67, 69-72, 76-86, 90-97, 101-109, 111-113, 116-123, 127 and 129 lack novelty under PCT Article 33(2) as being anticipated by Fuller *et al.* (US Patent 6,051,385, herein, "Fuller"). The claims are drawn to a method comprising incubating a mixture comprising at least one cell, a labeled invasin that encodes a detectable label, and a candidate agent under conditions wherein the labeled invasin can invade the cell; and detecting the detectable label within the cell, wherein an increase or decrease of detectable label in the cell due to the candidate agent indicates that the candidate agent modulates invasion of the cell by the invasin. The candidate agent may increase or decrease invasion of the cell by the labeled invasin. The agent can be a peptide, antibody or enzyme that associates with the labeled invasin. The invasin can be an enveloped virus, such as herpesvirus, that displays a preselected antigen on its surface. The preselected antigen may be a fusion protein containing a peptide. The detectable label is a fluorescent protein or an enzyme. The cell can be a mammalian cell, such as a human cell. The agent associates with a receptor. The incubation may include a specimen containing antibodies.

Fuller discloses methods of identifying and testing therapeutics against HSV infection, particularly compositions comprising receptors which enable cell specific entry of HSV. Fuller discloses a protein agent that confers the ability of HSV to infect and replicate in otherwise non-permissive cells. Also taught are vectors comprising nucleic acids encoding the HSV receptors, fragments and homologs thereof. Also disclosed is a porcine cell system which expresses a HSV receptor but not the endogenous HSV entry receptors (abstract). Libraries of compounds can be screened with Fuller's method, including antibodies capable of inhibiting human HSV virus entry by binding to receptors (col. 3, lines 25-30). Fuller also discloses the use of a reporter gene system which expresses visible markers that can be detected by auto-fluorescence. Also taught are purified antibodies, vaccines comprising viral receptor antigens such as epitopes. Cell lines disclosed are B5 transfected cells used to screen anti-HSV agents (col. 38, lines 10-36).

Claims 123-127 and 129 lack novelty under PCT Article 33(2) as being anticipated by Domínguez *et al.* (*J. Immunological Methods*, 1998, Vol.220, pages 115-121, herein, "Domínguez"). The claims are drawn to a kit comprising packaging material, an invasin that encodes a detectable label and/or a cell that the invasin can invade. The invasin is a vaccinia virus, the detectable label is an enzyme, such as beta-galactosidase or a fluorescent protein. Domínguez discloses green fluorescent protein expressed by a recombinant vaccinia virus the permits early detection of infected cells by flow cytometry (abstract). Domínguez's method uses packaging material, vaccinia and a detectable label that marks the presence of infected cells (page 116, materials and methods section).

Claims 7, 8, 38, 44, 46-58, 73, 87, 114 and 128 lack an inventive step under PCT Article 33(3) as being obvious over Fuller in view of Domínguez. The claims are drawn to a method of identifying candidate agents that modulate cell invasion by a virus, such as vaccinia (smallpox). The teachings of Fuller are summarized above. Fuller does not teach the use of vaccinia (smallpox) virus.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

However, Domínguez discloses the use of vaccinia virus that expresses GFP as an marker for viral infection. It would have been obvious to use Domínguez's vaccinia virus marker system as an invasin in Fuller's method. One would have been motivated by Domínguez's teaching that the vaccinia virus expressing GFP can be used to monitor infection quickly and conveniently. One would have had a reasonable expectation of success that Domínguez's marker system would have worked in Fuller's method because Fuller's method requires the use of a marker system to detect infection and Domínguez's system detects viral infection with a marker (GFP). The kit of claim 128 is disclosed by Domínguez with the exception of a HeLa cell. However, Fuller teaches that any cell can be used, even those cells that do not naturally express the desired receptor. The receptor can be engineered to be expressed on any clonal cell (Fuller, col. 3-4, bridging paragraph). One would have been motivated to use HeLa cells because they are a proliferative cell line. Therefore, the claims would have been obvious over Fuller in view of Domínguez.

Claims 64 and 68 lack an inventive step under PCT Article 33(3) as being obvious over Fuller in view of Rocancourt *et al.* (*J. Virology*, 1990, Vol. 64, No. 6, pages 2660-2668, herein, "Rocancourt"). The claims are drawn to a method comprising incubating a mixture comprising, an invasin that encodes a detectable label and has a preselected antigen on its surface, a specimen suspected of containing an antibody that binds to the preselected antigen, and at least one cell, under conditions wherein the invasin can invade the cell; and detecting the detectable label within the cell; wherein a decrease in the detectable label in the cell due to the specimen indicates that the specimen contains an antibody that binds to the preselected antigen. Specifically, the preselected antigen is a peptide, HIV gp120. The teachings of Fuller are summarized above. Fuller is silent on the presence of HIV gp120 as the receptor. However, Rocancourt discloses detection of HIV-infected cells by incubating cells that express beta-galactosidase when infected with HIV in the presence of an antiviral drug, such as a CD4-immunoglobulin chimera (which binds gp120). See pages 2665-2666, bridging paragraph. It would have been obvious to use Rocancourt's HIV-infected cells that express beta-galactosidase upon infection in Fuller's method to test antivirals. One would have been motivated to use Rocancourt's cells because they express a detectable marker upon infection, which accomplishes the same objective as Fuller's method. One would have had a reasonable expectation of success that the cells expressing beta-galactosidase and infected with HIV would have worked in Fuller's method because the cells express gp120 and would be detectable by the beta-galactosidase expression. Therefore, the claims would have been obvious over Fuller in view of Rocancourt.

Claims 11, 41, 75, 89, 99, 100 and 110 lack an inventive step under PCT Article 33(3) as being obvious over Fuller in view of Nir *et al.* (*Applied and Environmental Microbiology*, 1990, Vol. 56, No. 12, pages 3861-3866, herein, "Nir"). The claims are drawn to a method of determining candidate agents' ability to affect cell invasion by an invasin such as a bacterium. Fuller's teachings are summarized above. Fuller is silent on a method of identifying candidate agents that inhibit bacteria invasion of cells. However, Nir discloses a method of detecting bacteria and yeasts according to beta-galactosidase activity. It would have been obvious to use Fuller's teachings about candidate agents and labeled invasions with Nir's teachings regarding labeled bacteria. Fuller's method is applicable to other invasins in a general assay for candidate agents. One would have had a reasonable expectation of success that Nir's method for detecting bacteria would have worked in Fuller's method because Nir's bacteria are detectable by beta-galactosidase expression. Therefore, the claims would have been obvious over Fuller in view of Rocancourt.

Claims 9, 10, 39, 40, 74, 88, 98 and 115 lack an inventive step under PCT Article 33(3) as being obvious over Fuller in view of Quantin *et al.* (*PNAS USA*, 1992, Vol. 89, pages 2581-2584, herein, "Quantin"). The claims are drawn to a method of determining candidate agents' ability to affect cell invasion by an invasin such as a non-enveloped virus, such as an adenovirus. The teachings of Fuller are summarized above. Fuller is silent on the use of adenovirus. However, Quantin discloses the detection of adenovirus expressing beta-galactosidase in cells. It would have been obvious to use Quantin's adenovirus expressing beta-galactosidase in Fuller's method. One would have been motivated to determine agents that increase Quantin's adenovirus' ability to infect cells and express the desired gene in the adenovirus. One would have had a reasonable expectation of success that Quantin's adenovirus detection method would have worked in Fuller's method because the adenovirus is detectable in infected cells by beta-galactosidase marker. Therefore, the claims would have been obvious over Fuller in view of Quantin.

Claims 1-129 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------